Agricultural Chemical Safety Assessment: An Improved Toxicology Testing Paradigm

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Introduction

Knowledge of toxicology and testing capabilities has increased dramatically since many testing methodologies were originated. Moreover, human health assessment today calls for an increasing complexity and sophistication of science considerations such as an understanding of mechanisms of toxicity, special susceptibility of life stages, and risk from shorter-term or more intermittent exposures to agricultural chemicals.

In recent years, efforts have been made to tailor approaches to safety assessment to the use of certain types of products. Examples include cosmetics (European Commission) and medicines (ICH). While there are specific requirements for registering agricultural chemicals (US EPA and European Union), there has never been a systematic attempt to design a framework for their evaluation that employs studies tailored to exposure scenarios for which human health risk assessments are performed.

There is multi-sector, international interest in examining how the agricultural chemical safety assessment process could be improved. In 2000, the ILSI Health and Environmental Sciences Institute (HESI) formed the Agricultural Chemical Safety Assessment (ACSA) Technical Committee to design a toxicity testing scheme that would incorporate current understanding of pesticide toxicology and exposure and that would recognize the specificity of agricultural products. The mission of the Technical Committee was to develop a consensus across sectors (international governments, academia, industry, and non-profit organizations) on a scientifically credible and viable system that could be implemented today for evaluating the potential adverse effects of agricultural chemicals more efficiently, with greater accuracy and fewer artifacts, and using fewer animals.

Tiered Testing Approach

Three multi-sector, international task forces—ADME (absorption, distribution, metabolism, and excretion), Life Stages, and Systemic Toxicity—were established with the goal of creating one coherent scheme that is driven by science; has greater flexibility; incorporates selection of dosing based on kinetics and physiology; integrates evaluations for life stage effects, systemic toxicity, and kinetics; reduces and refines animal usage; and is guided by human exposure predictions.

ADME Task Force

The ADME Task Force developed an approach that integrates useful metabolic and kinetic data into the design and interpretation of toxicology studies on agricultural chemicals. *Basic* data are obtained for dose selection and toxicity study design, such as half-life determination. *Intermediate* data are used for study interpretation, absorbed dose estimates, and duration extrapolations. *Advanced* data support better understanding of a compound's mode of action, allow the evaluation of pharmacodynamic concordance, and develop other risk assessment applications, particularly route and interspecies extrapolations.

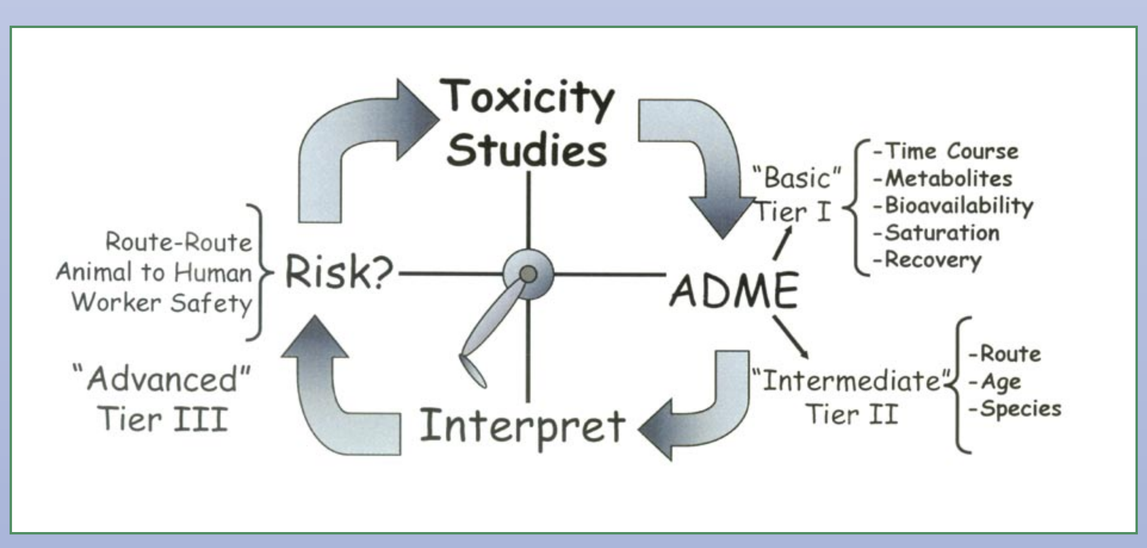

FIGURE 1
The iterative process for collecting ADME and toxicity data for use in risk assessment, illustrating the three tiers for ADME data collection.

Systemic Toxicity Task Force

The Systemic Toxicity Task Force developed an approach that ensures evaluation of all relevant toxicity parameters and identifies a hierarchy of study types, endpoints, and triggers that would be used in a tiered approach. Included are studies for deriving reference doses for less-than-lifetime periods of human exposure, a comprehensive 28-rat day study, a 90-day dog study, a 24-month rat study with a 12-month interim sacrifice, options to augment studies with satellite groups to explore specific endpoints, and specialized investigations if a second tier of testing becomes necessary.

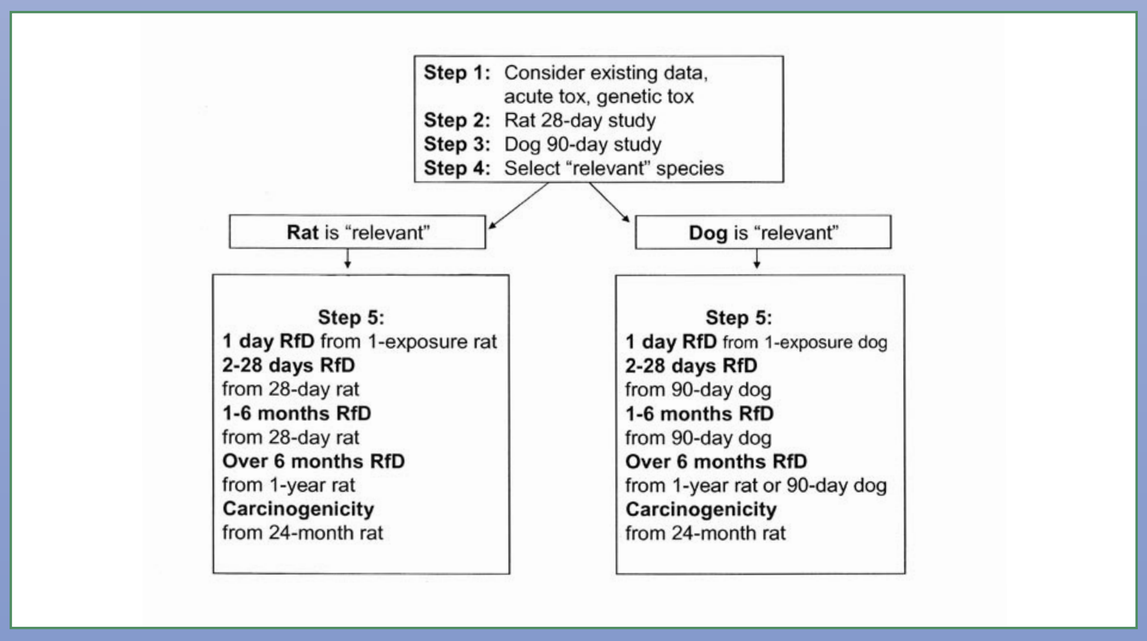

FIGURE 2
Diagrammatic representation of the systemic toxicity strategy

Life Stages Task Force

The Life Stages Task Force developed an approach to ensure adequate coverage of all vulnerable life stages, and identifies a hierarchy of study types, endpoints, and triggers that would be used in a tiered approach. Included is assessment of systemic toxicity in young adults as a consequence of pre- and early post-natal exposure; use of a one-generation design to obtain comprehensive data while limiting the number of animals involved; assessment of prenatal development in a second species; evaluation of developmental neurotoxicity and immunotoxicity; and the use of fewer animals compared to the conduct of separate developmental neurotoxicity, developmental immunotoxicity, and two-generation reproduction studies.

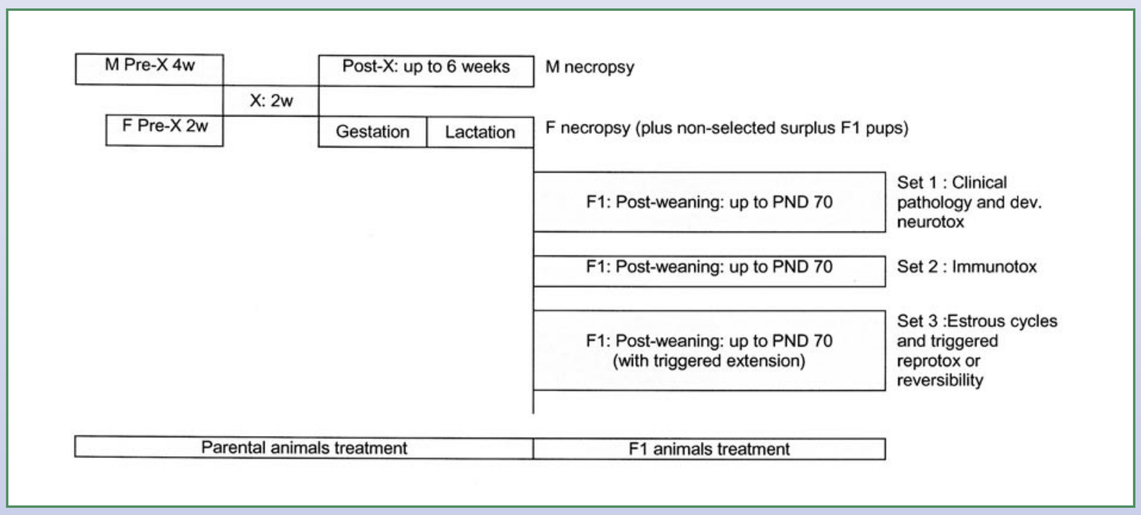

FIGURE 3
F1-extended one-generation study in the rat (Life Stages Tier 1)

Conclusion

The proposed tiered testing scheme is intended to provide assurance of safety equal to the current approach, while focusing resources on those studies which will be used in the risk assessment process. Among the advantages of the proposed scheme are the following:

- Based on the results of early studies, resources can be devoted to exploring endpoints that are likely to be critical and to test species that are determined to be more relevant.
- Depending on how many Tier 2 tests are triggered, it is possible to reduce the number of animals used for testing from over 6,000 in the current approach (including all offspring in reproductive and developmental testing) to 2,000-3,000.
- Hazard endpoints are better characterized with exposure scenarios of interest.
- Greater emphasis is placed on ADME studies than currently exists to better predict internal dose.

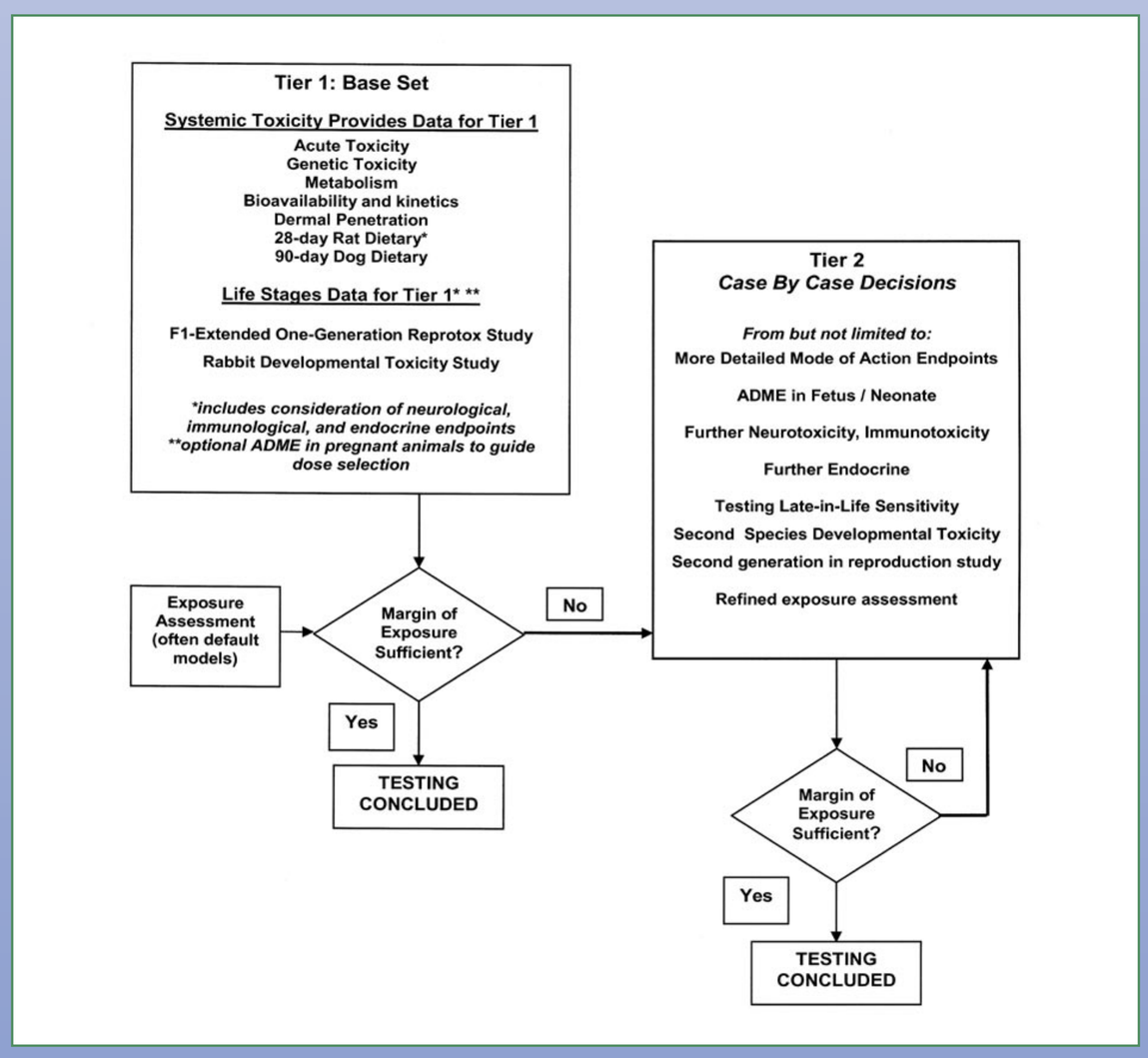

FIGURE 4
Overview of the HESI ACSA Proposed Tiered Testing Approach

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